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Cutaneous and Coronary Flow Reserve in Patients With Microvascular Angina

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Microvascular angina is characterized by exercise-induced angina in patients with normal coronary arteries and reduced coronary flow reserve. Recently, a generalized disorder of abnormal vascular reactivity in microvascular angina has been postulated. Therefore, coronary flow reserve was determined by the coronary sinus thermodilution technique and compared with the cutaneous flux ratio in 6 control subjects (group 1) and 12 patients with microvascular angina (group 2).

Coronary flow reserve was calculated from maximal coronary flow after 0.5 mg/kg of dipyridamole divided by flow at rest. Cutaneous flow ratio was estimated by laser Doppler fluxmetry (right forearm) before and after 4 min of suprasystolic blood pressure occlusion. Coronary flow at rest was identical in the two groups, but after maximal vasodilation with dipyridamole, coronary flow was higher in group 1 than in group 2 ($p < 0.05$). Coronary flow reserve differed significantly between the two groups (2.9 in group 1 and 1.3 in group 2; $p < 0.001$). Cutaneous Doppler flux at rest was higher in group 1 than in group 2 ($p < 0.05$). However, the hyperemic response was identical in both groups.

It is concluded that the cutaneous flux ratio in patients with microvascular angina is not impaired. Local peripheral vasomotor tone appears to be increased in patients with microvascular angina because cutaneous flow at rest is reduced. Thus, a generalized disorder of abnormal vascular reactivity cannot be confirmed in patients with microvascular angina.

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Microvascular angina is characterized by ischemia-like symptoms and normal coronary arteries. Typically, coronary flow reserve is impaired and myocardial oxygen extraction and lactate metabolism are abnormal during rapid atrial pacing (1,2). The exact pathophysiologic mechanism of this syndrome is not known, but it might be caused by abnormal vascular reactivity (3) or abnormal myocardial metabolism (2).

Recently, using strain gauge plethysmography to study the hyperemic response of the forearm after transient ischemia, Specchia et al. (4) showed that microvascular angina is part of a generalized disturbance of the vasodilator response of the small arteries that involves the peripheral vascular bed as well as the coronary arteries. The purpose of this study was to examine cutaneous and coronary flow reserve in healthy control subjects and a group of patients with microvascular angina.

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Methods

Study patients. A total of 18 patients were included in the present study. There were 14 men and 4 women.

The following inclusion criteria were used for patients with microvascular angina: 1) chest pain syndrome with typical or atypical angina pectoris; 2) ST segment depression (≥0.1 mV) during upright exercise testing; 3) normal coronary arteries during diagnostic arteriography; and 4) reduced coronary flow reserve as determined by coronary sinus thermodilution technique.

Only patients with normal blood pressure and without evidence of left ventricular hypertrophy on the standard 12-lead electrocardiogram were included. Similar inclusion criteria have been used by others (4,5) because classification of patients with microvascular angina on the basis of exercise test results is often misleading; thus, reduced coronary flow reserve has been found to be the most reliable diagnostic test for identifying patients with microvascular angina (1–5).

Patient groups. Patients were classified in two groups. Group 1 consisted of six control subjects with normal coronary arteries and normal coronary flow reserve (≥2). There were two women and four men with a mean age of 50 ± 9 years (range 33 to 59). Group 2 consisted of 12 patients with microvascular angina, that is, normal coronary

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arteries and reduced coronary flow reserve (<2). There were 2 women and 10 men with a mean age of 51 ± 9 years (range 38 to 62). No patients had Raynaud's phenomenon.

Study Protocol. *Exercise testing.* All patients underwent upright exercise testing while receiving their regular medical therapy. Heart rate, mean aortic pressure and rate-pressure product (heart rate multiplied by systolic blood pressure) were calculated in all patients at rest and during maximal exercise. The ST segment depression was determined under steady state conditions in the precordial lead with the most prominent ST segment depression.

Cardiac catheterization. All patients gave informed consent before cardiac catheterization, which was performed for diagnostic purposes. All drugs were discontinued for 12 to 24 h before the procedure. Biplane left ventricular angiography was performed according to our standard technique (6,7). Left ventricular volumes were calculated by using the area-length method. Left ventricular muscle mass was determined by the technique of Rackley et al. (8). Diagnostic coronary arteriography was carried out with the Judkins technique.

Coronary blood flow measurements. Coronary sinus blood flow was measured by the coronary sinus thermodilution technique (7,9) on an outpatient basis 5 to 72 days (mean 39) after coronary arteriography. All drugs were discontinued for 48 to 72 h before the study and patients were in a fasting state. A 7F thermodilution catheter (CCS-7U-90A or B, Webster Laboratory) was introduced from the right femoral vein into the coronary sinus. The correct position was checked by measuring oxygen saturation (at rest and after dipyridamole infusion) and by injection of small amounts of contrast medium. The signals of the external (mixing temperature of blood and saline solution) and internal (temperature of the injected saline solution) thermistors were recorded on an oscillograph (model VR-12, Electronics for Medicine) at a paper speed of 5 mm/s. Then, saline solution at room temperature was infused through the thermodilution catheter at a rate of 50 ml/min and coronary sinus flow (ml) was calculated according to the method of Ganz et al. (9). Coronary flow was normalized per 100 g of muscle mass. Coronary resistance (R, mm Hg·min·100 g/ml) was calculated according to the following equation: $R = (AoP - CSP)/CBF_n$, where AoP is mean aortic pressure by the cuff method (mm Hg), CSP is mean coronary sinus pressure (mm Hg) and CBF_n is coronary sinus blood flow per 100 g of muscle mass (ml/min·100 g).

Coronary sinus outflow was determined at rest and after infusion of 0.5 mg/kg of dipyridamole over 15 min. This duration of infusion was chosen to minimize the systemic effects of dipyridamole on heart rate and blood pressure (10,11).

Coronary flow ratio (coronary flow reserve) was calculated as coronary sinus flow after dipyridamole infusion divided by blood flow at rest. Coronary resistance ratio was determined from the resistance at rest divided by the resistance after dipyridamole infusion.

Cutaneous flow measurements. Cutaneous blood flow was determined by laser Doppler fluxmetry. This method allows semiquantitative measurements of skin perfusion. The laser Doppler signal is obtained from a laser device (2-mW helium-neon laser, emitting light at a wavelength of 632.8 nm; Periflux PF3, Perimed) and corresponds to the red cell flux. It is defined as the product of the number of moving red blood cells under the probe multiplied by their velocity (12,13). The signal is proportional to blood flow but is not an absolute measure of flow; it is expressed in arbitrary units (AU). For standardization of skin temperature (35.9°C), we used a special triple probe (14) that has a temperature feedback control.

In all patients, medication was discontinued for ≥72 h before the investigation. The laser Doppler probe was fixed to the skin of the medial right forearm with adhesive ring-tape. A sphygmomanometric cuff was attached above the elbow and blood pressure and heart rate were measured. After a rest period of 20 min with the patient supine, continuous recording of the laser Doppler signal at rest was performed on a strip chart recorder (Gould Brush 2600S). Suprasystolic compression (50 mm Hg above the systolic blood pressure for 4 min) was then performed, during which the laser Doppler signal decreased to the biologic zero value. After rapid cuff deflation, postocclusive reactive hyperemia was continuously recorded (Fig. 1). An occlusion of ≥3 min was previously shown (4) to induce maximal cutaneous hyperemic flow to the skin (15) or near maximal flow in the forearm. Baseline laser Doppler signals were then recorded again and the cold pressor test was started with the patient's left hand immersed in ice-cold water for 2 min.

The cutaneous vasodilator ratio was calculated as the ratio of maximal hyperemic laser Doppler signal divided by the value at rest.

Statistical analysis. Data are reported as mean value ± 1 SD. Comparisons were made by using the unpaired Student *t* test and the paired Student *t* test where appropriate (95% probability).

Results

Clinical data. In group 1, three patients presented with typical and three patients with atypical chest pain. In group 2, nine patients had typical and three had atypical chest pain.

Medical therapy. Four patients in group 1 and seven in group 2 were receiving combined therapy with a beta-adrenergic blocking agent and a calcium channel antagonist. A small subgroup of patients (one in group 1 and five in group 2) received monotherapy with either a beta-blocker or a calcium channel antagonist or nitrate. One patient had no medication.

Exercise testing. Heart rate, mean arterial pressure, rate-pressure product and ST segment depression at rest were identical in the two groups (Table 1). The corresponding values during maximal exercise were also comparable. The reason for termination of the exercise test was fatigue in 50%

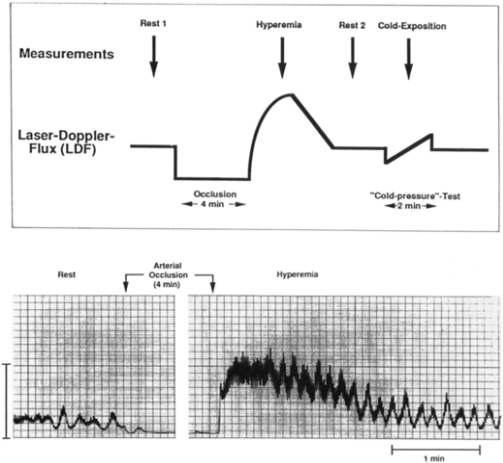

Figure 1. Upper panel, Protocol for the cutaneous flow measurements. After a control run, right brachial artery occlusion was performed by suprasystolic inflation of a cuff for 4 min. Deflation of the cuff resulted in an instantaneous postocclusive hyperemic response followed by a gradual normalization of flow during the next 4 to 6 min and return of the signal to the baseline level. After a second control run, the contralateral arm was immersed in ice-cold water for 2 min. **Lower panel,** Typical strip chart recording from a control subject, with the laser Doppler signal displayed as a function of time. The ordinate expresses the amplitude of the signal in arbitrary units (AU). Note the induction of low frequency, high amplitude flux motion waves in the hyperemic phase. The maximal postocclusive hyperemic response was 4.3 times the rest value in this example.

of the patients in group 1 and 75% of those in group 2. Maximal ST segment depression was slightly more pronounced in group 1 (mean 0.18 mV) than in group 2 (mean 0.13 mV; p = NS).

Hemodynamic and angiographic data. Heart rate and left ventricular end-diastolic and systolic pressure were similar in both groups (Table 2). Left ventricular ejection fraction was 68% in group 1 and 66% in group 2 (lower limit of normality ≥57%). Left ventricular end-diastolic volume index was slightly higher in group 1 than in group 2 (92 vs. 78 ml/m^2, p = NS). Left ventricular muscle mass index was within the normal limits in both groups (range of normality 56 to 135 g/m^2, mean 94 ± 19).

Coronary blood flow and flow reserve. Cuff blood pressure and heart rate obtained before and after dipyridamole infusion (Table 3) were identical at rest in both groups; however, heart rate increased significantly after dipyridamole. Mean aortic pressure decreased from 101 to 96 mm Hg (p < 0.001) after dipyridamole infusion in group 1 but remained unchanged in group 2 (106 to 102 mm Hg, p = NS).

Coronary blood flow at rest (Fig. 2) was 138 ml/min in group 1 and 176 ml/min in group 2. After dipyridamole infusion, it increased to 422 ml/min (p < 0.05) in group 1 and to 221 ml/min (p < 0.01) in group 2. Coronary flow reserve was 2.9 in group 1 and 1.3 in group 2 (p < 0.001). There was an outlier with a supernormal flow of 859 ml/min during dipyridamole infusion; if this outlier was excluded, there was only borderline significance (p < 0.07) for the difference in hyperemic flow between groups 1 and 2 (Fig. 2). This outlier was not observed when coronary sinus oxygen saturation values were compared between the two groups (see below).

Coronary sinus oxygen saturation (Fig. 2) at rest was

Table 1. Upright Exercise Testing in 18 Patients

		Rest				Exercise					
	No.	HR	RR_{mean}	ST↓	RPP	WL_{max}	$WL\%_{max}$	HR	RR_{mean}	RPP	ST↓	Sy
Group 1	6	68 ± 15	100 ± 8	0.04 ± 0.05	86 ± 19	141 ± 48	93 ± 16	143 ± 31	114 ± 16	232 ± 60	0.18 ± 0.12	3 FT 3A
Group 2	12	74 ± 16	105 ± 8	0.02 ± 0.04	98 ± 22	143 ± 42	91 ± 18	144 ± 17	114 ± 14	241 ± 53	0.13 ± 0.12	9 FT 3A

All values are expressed as mean value ± SD. p = NS, group 1 versus group 2 for all measurements. A = anginal pain; FT = fatigue; HR = heart rate (beats/min); RPP = rate-pressure product (mm Hg·100/min); RR_{mean} = mean brachial blood pressure (mm Hg); ST↓ = ST segment depression (mV); Sy = symptoms; WL_{max} = maximal working capacity (W); $WL\%_{max}$ = percent of predicted maximal working capacity.

Table 2. Hemodynamic and Angiographic Data From 18 Patients

	No.	BSA	HR	LVSP	LVEDP	EDVI	EF	LMMI
Group 1	6	1.82 ± 0.11	62 ± 13	129 ± 23	13 ± 5	92 ± 9	68 ± 8	83 ± 13
Group 2	12	1.88 ± 0.14	66 ± 10	129 ± 21	13 ± 5	78 ± 17	66 ± 6	84 ± 8

All values are expressed as mean value ± SD. p = NS, group 1 versus group 2 for all measurements. BSA = body surface area (m^2); EDVI = end-diastolic volume index (ml/m^2); EF = ejection fraction (%); HR = heart rate (beats/min); LMMI = left ventricular muscle mass (g/m^2); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular systolic pressure (mm Hg).

34.7 ± 5.8% in group 1 and 30.5 ± 5.9% in group 2 and increased significantly in both groups to 72 ± 7% in group 1 and 51% ± 12% in group 2. However, mean oxygen saturation was lower after dipyridamole infusion in group 2 than group 1 ($p < 0.002$).

Coronary resistance was similar in both groups (p = NS). After dipyridamole infusion, it decreased ($p < 0.001$), but the resistance ratio was smaller in group 2 (1.3) than in group 1 (3.1; $p < 0.001$) (Fig. 3).

Cutaneous flow and cutaneous flow reserve. Cutaneous blood flow was significantly ($p < 0.05$) higher in group 1 than in group 2 (Table 4). The postocclusive hyperemic flow increased to similar values in both groups (p = NS). The flow ratio was 2.9 in group 1 and 4.6 in group 2 (p = NS). By 4 to 6 min after release of the occlusion, cutaneous flow had returned to control values, but flow at rest remained elevated in group 1 compared with the level in group 2 ($p < 0.05$). During the cold pressor test, cutaneous flow remained unchanged. When women were excluded from the comparison, there was no difference in cutaneous flow ratio (3.0 in group 1 vs. 5.0 in group 2).

Discussion

Microvascular angina is characterized by chest pain with ST segment depression during exercise and a reduced coronary flow reserve in the presence of normal coronary arteries. The entity was first described as syndrome X by Kemp in 1973 (16). Since then, numerous investigators (17–20) have studied this syndrome and abnormalities of left ventricular function, perfusion defects, lactate production and abnormal histologic findings have been reported.

More recently, an abnormal vascular response of the microvasculature (3,5) and an abnormal reaction of the distal epicardial coronary arteries to physical exercise were reported (7). Sax et al. (4) postulated a generalized disorder of the microvasculature with impaired coronary and peripheral vasodilator responses. The purpose of the present study was to test whether this hypothesis is also valid for the cutaneous vasculature and to determine both coronary and cutaneous blood flow reserve in a control group and a group of patients with microvascular angina.

Coronary and cutaneous vasodilator reserve. The definition of microvascular angina includes an abnormal coronary flow reserve (ratio <2), which was found in 12 of our 18 patients with normal coronary arteries. The reduction in coronary flow reserve was comparable to values observed in patients with severe coronary artery disease (21) and in contrast to the flow reserve in normal epicardial coronary arteries, thus suggesting an abnormality of the coronary microvasculature. A disorder of the microvasculature was postulated by Sax et al. (4), but the vasodilator reserve of the cutaneous microvasculature was normal in the present study. Apparently, the abnormal response of the microvasculature to the pharmacologic dilator stimulus is limited to the coronary arteries and does not include the skin vessels. The reduced cutaneous flow under rest conditions in patients with microvascular angina could be explained by increased

Table 3. Coronary Blood Flow Measurements in 18 Patients

	No.	HR	MAP	CBF	CFR	CBF_n	CR	CR_R/CR_D	CSS
Group 1									
R	6	68 ± 13	101 ± 8	138 ± 44	—	95 ± 27	1.1 ± 0.3	—	34.7 ± 5.8
D	6	86 ± 17	96 ± 7	422 ± 253	2.9 ± 0.9	282 ± 140	0.4 ± 0.2	3.1 ± 1	72 ± 7
p Value (R vs. D)		< 0.01	< 0.001	< 0.05	—	< 0.05	< 0.001	—	< 0.001
Group 2									
R	12	79 ± 12	106 ± 11	176 ± 65	—	113 ± 42	0.9 ± 0.6	—	30.5 ± 5.9
D	12	89 ± 11	102 ± 17	221 ± 90	1.3 ± 0.2	143 ± 58	0.7 ± 0.4	1.3 ± 0.3	51.1 ± 12
p Value (R vs. D)		< 0.001	NS	< 0.01	—	< 0.01	< 0.05	—	< 0.001
p Value (group 1 vs. group 2)									
R vs. R		NS	NS	NS	—	NS	NS	—	NS
D vs. D		NS	NS	< 0.05	(< 0.001)	< 0.01	NS	(< 0.001)	< 0.002

All values are expressed as mean value ± SD. CBF = coronary blood flow (ml/min); CBF_n = normalized coronary blood flow (ml/min per 100 g muscle mass); CFR = coronary flow reserve; CR = coronary resistance (mm Hg·min·100 g/ml); CR_R/CR_D = coronary resistance ratio; CSS = coronary sinus oxygen saturation (%); D = dipyridamole; HR = heart rate (beats/min); MAP = mean aortic blood pressure (mm Hg); R = rest.

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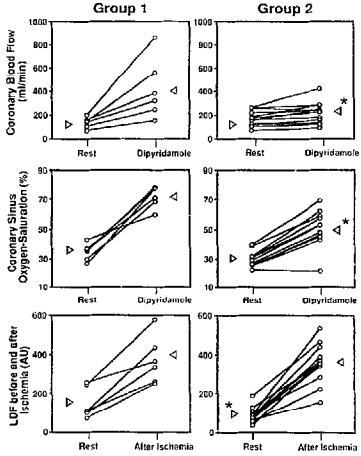

Figure 2. Changes in coronary blood flow (**top panel**) and coronary sinus oxygen saturation (**middle panel**, before (Rest) and after administration of dipyridamole and changes in the laser Doppler signal before and after ischemia (**bottom panel**). The diagrams on the **left** represent findings in the control subjects (group 1) and those on the **right** show measurements in patients with microvascular angina (group 2). After dipyridamole infusion, there was a marked increase in coronary blood flow and coronary sinus oxygen saturation in group 1 compared with values in group 2. Cutaneous flow at rest was higher in group 1 than in group 2, but all patients had a marked postocclusive increase in cutaneous flow. AU = arbitrary units; LDF = laser Doppler flux; **open triangles** = mean values. *$p < 0.05$ group 1 versus group 2.

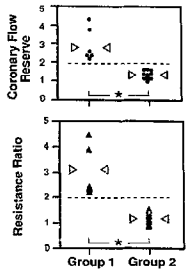

Figure 3. Coronary flow reserve (**upper panel**) and coronary resistance ratio (**lower panel**) in control subjects (group 1) and in patients with microvascular angina (group 2). All control subjects had a coronary flow reserve ≥2. Patients with microvascular angina had a severely reduced flow reserve. The resistance ratio was lower in group 2 than in group 1. **Open triangles** = mean values. *$p < 0.001$.

sympathetic outflow to the limbs, as reported in normal female volunteers (13,22). However, the vasodilator response was not impaired in these subjects, suggesting that changes in basal sympathetic tone may affect rest but not maximal cutaneous blood flow. A recent study by Cooke et al. (13) demonstrated that basal flow was approximately two times greater in men than in women; however, maneuvers such as warming, deep breathing and mental stress reversed the pattern of cutaneous flow. When women were excluded from the analysis in our study, cutaneous flow at rest was still smaller in group 2, but the hyperemic response remained similar. Thus, a gender difference does not explain our observation of a normal cutaneous flow ratio in the presence of reduced coronary flow reserve.

Comparison of methods for peripheral flow measurement. Sax et al. (4) used mercury-in-Silastic strain gauge plethysmography in their study; this method allows noncontinuous measurement of the whole forearm blood flow and therefore reflects mainly skeletal muscle blood flow. In contrast, laser Doppler fluxmetry permits continuous measurements but reflects skin blood flow only, with a hemispheric sample volume restricted to a small radius of approximately 1 mm (12,23).

Comparisons between laser Doppler flux measurements and plethysmographic data have been performed at rest, after increasing body skin temperature and after occlusion of the blood flow to the arm (24). A good correlation was found between results of laser Doppler fluxmetry and those of plethysmography of the forearm ($r = 0.94$ to 0.98); however, the relation varied among studies and regions. The nature of flow changes (that is, an increase or decrease in flow) could be assessed with good reproducibility by laser Doppler fluxmetry. A similar but a slightly poorer correlation was reported (12) between results of laser Doppler fluxmetry and those of the xenon-133 clearance technique ($r = 0.82$). Some of the variability observed between laser Doppler flux measurements and plethysmographic findings can be attributed to the variability in the number of microvessels within the sample volume. Nevertheless, laser Doppler fluxmetry appears to be a reliable technique for assessing cutaneous flow reserve.

Pathophysiologic mechanisms. Several mechanisms of microvascular angina have been suggested, including small vessel disease (3,5,19), abnormal cardiac metabolism (1–3,16), abnormal response of the microvasculature (2,3,5), abnormal sensitivity (25), abnormal endothelial function and coronary vasospasm (26). Which of these mechanisms is responsible for the occurrence of microvascular angina cannot be answered by the present study. However, we found no involvement of the skin microvasculature in our

Table 4. Cutaneous Flow Measurements in 18 Patients

	No.	HR	MAP	Flow 1	Ratio 1	Flow 2	Ratio 2
Group 1							
R	6	64 ± 10	105 ± 12	148 ± 82	—	155 ± 82	—
H	6	—	—	373 ± 122	2.9 ± 1	—	—
CPT	6	—	—	—	—	174 ± 111	1.1 ± 0.4
p Value				—			
R vs. H		—	—	< 0.01	—	—	—
R vs. CPT		—	—	—	—	NS	—
Group 2							
R	12	68 ± 14	107 ± 11	87 ± 39	—	95 ± 39	—
H	12	—	—	357 ± 102	4.6 ± 2.1	—	—
CPT	12	—	—	—	—	103 ± 43	1.1 ± 0.4
p Value							
R vs. H		—	—	< 0.001	—	—	—
R vs. CPT		—	—	—	—	NS	—
p Value (group 1 vs. group 2)							
R vs. R		NS	NS	< 0.05	—	< 0.05	—
H vs. H		—	—	NS	NS	—	—
CPT vs. CPT		—	—	—	—	NS	NS

CPT = cold pressor test; Flow 1 = flow before occlusion (arbitrary units [AU]); Flow 2 = flow at rest before the cold pressor test (AU); H = postocclusive hyperemia; HR = heart rate (beats/min); MAP = mean aortic blood pressure (mm Hg); R = rest; Ratio 1 = ratio of postocclusive hyperemic flow versus flow at rest; Ratio 2 = ratio of flow during the cold pressor test versus flow at rest.

patients. The abnormal response of the arteries to the vasodilator stimulus seems to be limited to the heart. However, a reduced blood flow ratio for skeletal muscle cannot be excluded by laser Doppler measurements because these data represent only skin perfusion. A generalized disorder of the vasculature is excluded by the fact that successful pharmacologic vasodilation of the coronary arteries in control subjects and diminished response in patients with microvascular angina were not accompanied by changes in skin perfusion during reactive hyperemia at the microvascular level.

Limitations of the study. The coronary sinus thermodilution technique was used to measure total coronary sinus blood flow. Although this method is unable to measure perfusion in specific transmural layers and different left ventricular regions or rapid changes in coronary blood flow, Ganz et al. (9) observed a high correlation between coronary sinus flow measured by this technique and by timed collection of venous blood. According to Marcus et al. (27), this technique is adequate for measuring relatively slow and large changes (>30%) in coronary blood flow. The increase in coronary blood flow after dipyridamole infusion was clearly >30% in group 1 (306%) and moderate (only 26%) or nonexistent in group 2. Thus, the observations of normal (group 1) or reduced (group 2) flow reserve are certainly correct and not subject to methodologic errors. A major advantage of this method is that it can be applied in ambulatory patients, which is not possible with the use of intracoronary Doppler flow catheters and administration of papaverine as the hyperemic stimulus.

A relatively small dose of dipyridamole (0.5 mg/kg) was administered more slowly (15 vs. 4 to 10 min) than in other studies (5,28,29). The slow infusion was chosen to minimize the systemic effect on heart rate and blood pressure (10,11). This prolonged administration might explain why coronary flow reserve in control subjects was relatively low, the lowest being 2.3. However, others (5,28,29) have reported similar values. Recent studies (28,30,31) have shown that the "usual" intravenous dose of dipyridamole is frequently lower than that of intracoronary papaverine. For example, Rossen et al. (28) found a coronary flow reserve <2 after dipyridamole infusion in 25% of their patients, whereas the same patients had normal flow reserve with papaverine. Thus, some patients in our group 2 might have been nonresponders to dipyridamole and might not have true microvascular angina. Conversely, because of the short half-life of papaverine and its strong systemic effects, this drug must be infused by means of intracoronary administration.

Unlike plethysmography (32) and the xenon-133 clearance technique (33), which measure global blood flow in the limb including skin (approximately 6%), muscle (approximately 74%) and bones and fat tissue (approximately 20%), laser Doppler fluxmetry is confined to a small region of the skin with a variable number of microvessels. However, validation studies (12,24) have demonstrated satisfactory correlations with standard reference techniques. Thus, clinical application of the laser Doppler technique for assessing cutaneous flow seems to be justified. All measurements were performed under standardized conditions to minimize the side effects of increased sympathetic activity or changes in skin temperature (13,14).

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